

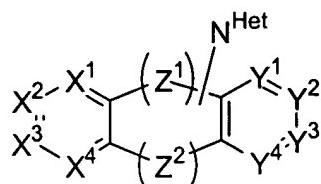
Amendments to the Claims:

This listing of claims will replace all prior versions, and listings of claims in the application:

Listing of Claims:

Claims 1-4 (canceled).

Claim 5 (previously presented): A method for inhibiting dissemination of CMV in a human, comprising administering to the human an effective amount of a compound which blocks or inhibits the binding of a chemokine to a US28 receptor or a US28 receptor fragment wherein said administering slows the progression of CMV viral dissemination in the human and wherein the compound has the formula:



wherein

X¹, X², X³ and X⁴ are each independently members selected from the group consisting of N and C-R¹, wherein R¹ is a member selected from the group consisting of H, halogen, (C₁-C₄)alkyl, (C₁-C₄)alkoxy, (C₁-C₄)haloalkyl, (C₁-C₄)haloalkoxy, nitro, cyano, (C₁-C₄)acyl, amino, (C₁-C₄)alkylamino, and di(C₁-C₄)alkylamino;

Y¹, Y², Y³ and Y⁴ are each independently members selected from the group consisting of N and C-R², wherein R² is a member selected from the group consisting of H, halogen, (C₁-C₄)alkyl, (C₁-C₄)alkoxy, (C₁-C₄)haloalkyl, (C₁-C₄)haloalkoxy, nitro, cyano, (C₁-C₄)acyl, amino, (C₁-C₄)alkylamino, and di(C₁-C₄)alkylamino;

Z^1 is a divalent moiety selected from the group consisting of (C_1 - C_3)alkylene;

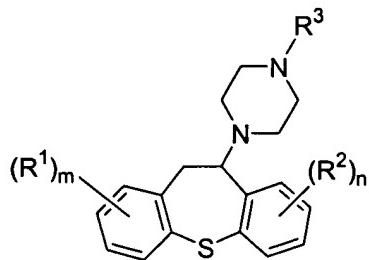
Z^2 is a divalent moiety selected from the group consisting of -O-, -S- and -N(R^3)- wherein R^3 is a member selected from the group consisting of H, halogen, (C_1 - C_4)alkyl, (C_1 - C_4)alkoxy, (C_1 - C_4)haloalkyl, (C_1 - C_4)haloalkoxy, nitro, cyano, (C_1 - C_4)acyl, amino, (C_1 - C_4)alkylamino, and di(C_1 - C_4)alkylamino; and

N^{Het} is a substituted or unsubstituted 4-, 5-, 6-, or 7-membered nitrogen heterocycle.

Claims 6 -7 (canceled).

Claim 8 (previously presented): A method in accordance with claim 5, wherein X^1 , X^3 , X^4 , Y^1 , Y^2 , Y^3 and Y^4 are all CH; Z^2 is -S-, and N^{Het} is a substituted 6-membered nitrogen heterocycle.

Claim 9 (original): A method in accordance with claim 5, wherein said compound has the formula:



wherein

the subscripts m and n are independently integers of from 0 to 3;

R^1 and R^2 are substituents independently selected from the group consisting of halogen, (C_1 - C_4)alkyl, (C_1 - C_4)alkoxy, (C_1 - C_4)alkylthio, (C_1 - C_4)haloalkyl, (C_1 - C_4)haloalkoxy, nitro, cyano, (C_1 - C_4)acyl, amino, (C_1 - C_4)alkylamino, and di(C_1 - C_4)alkylamino; and

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R^3 is a substituent selected from the group consisting of (C_1-C_4) alkyl, (C_1-C_4) haloalkyl and (C_1-C_4) acyl.

Claim 10 (original): A method in accordance with claim 9, wherein m is 0 and n is 1.

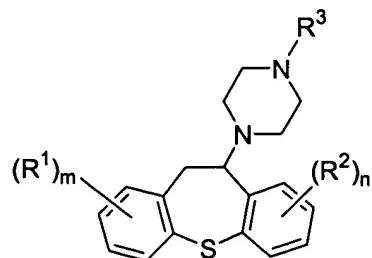
Claim 11 (original): A method in accordance with claim 9, wherein m is 0, n is 1 and R^2 is selected from the group consisting of halogen, (C_1-C_4) alkyl, (C_1-C_4) alkoxy, (C_1-C_4) alkylthio and (C_1-C_4) haloalkyl.

Claim 12 (original): A method in accordance with claim 9, wherein m is 0, n is 1 and R^2 is selected from the group consisting of halogen and (C_1-C_4) alkylthio.

Claim 13 (original): A method in accordance with claim 5, wherein said compound is selected from the group consisting of methiothepin, octoclothepin and pharmaceutically acceptable salts thereof.

Claims 14 -28 (canceled).

Claim 29 (previously presented): A method for treating CMV infection in a human, comprising administering to the human an effective amount of a US 28 receptor modulator capable of blocking or inhibiting the binding of a chemokine to the US28 receptor wherein said administering slows the progression of CMV dissemination in the human and wherein said compound has the formula:



wherein

the subscripts m and n are independently integers of from 0 to 3;

R¹ and R² are substituents independently selected from the group consisting of halogen, (C₁-C₄)alkyl, (C₁-C₄)alkoxy, (C₁-C₄)alkylthio, (C₁-C₄)haloalkyl, (C₁-C₄)haloalkoxy, nitro, cyano, (C₁-C₄)acyl, amino, (C₁-C₄)alkylamino, and di(C₁-C₄)alkylamino; and

R³ is a substituent selected from the group consisting of (C₁-C₄)alkyl, (C₁-C₄)haloalkyl and (C₁-C₄)acyl.

Claim 30 (canceled).

Claim 31 (previously presented): A method in accordance with claim 29, wherein m is 0 and n is 1.

Claim 32 (previously presented): A method in accordance with claim 29, wherein m is 0, n is 1 and R² is selected from the group consisting of halogen, (C₁-C₄)alkyl, (C₁-C₄)alkoxy, (C₁-C₄)alkylthio and (C₁-C₄)haloalkyl.

Claim 33 (previously presented): A method in accordance with claim 32, wherein m is 0, n is 1 and R² is selected from the group consisting of halogen and (C₁-C₄)alkylthio.

Claim 34 (previously presented): A method in accordance with claim 29, wherein said compound is selected from the group consisting of methiothepin, octoclothepin and pharmaceutically acceptable salts thereof.

Claim 35 (previously presented): A method in accordance with claim 29, wherein the molecular weight is between 300 and 600 daltons.

Claim 36 (previously presented): A method in accordance with claim 5, wherein the molecular weight is between 300 and 600 daltons.

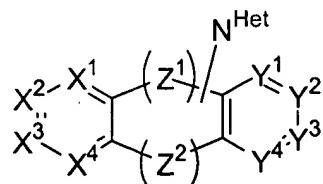
Claim 37 (previously presented): A method in accordance with claim 29, wherein said method the progression of viral dissemination via a CMV-infected leukocyte is slowed.

Claim 38 (previously presented): A method in accordance with claim 5, wherein said method the progression of viral dissemination via a CMV-infected leukocyte is slowed.

Claim 39 (previously presented): A method of claim 29, wherein the chemokine is fractalkine.

Claim 40 (previously presented): A method of claim 5, wherein the chemokine is fractalkine.

Claim 41 (new): A method of treating a patient for CMV infection, said method comprising determining if the patient is infected with CMV and if the patient is infected with CMV administering a compound of the formula:



wherein

X¹, X², X³ and X⁴ are each independently members selected from the group consisting of N and C-R¹, wherein R¹ is a member selected from the group consisting of H, halogen, (C₁-C₄)alkyl, (C₁-C₄)alkoxy, (C₁-C₄)haloalkyl, (C₁-C₄)haloalkoxy, nitro, cyano, (C₁-C₄)acyl, amino, (C₁-C₄)alkylamino, and di(C₁-C₄)alkylamino;

Y¹, Y², Y³ and Y⁴ are each independently members selected from the group consisting of N and C-R², wherein R² is a member selected from the group consisting of H, halogen, (C₁-C₄)alkyl, (C₁-C₄)alkoxy, (C₁-C₄)haloalkyl, (C₁-C₄)haloalkoxy, nitro, cyano, (C₁-C₄)acyl, amino, (C₁-C₄)alkylamino, and di(C₁-C₄)alkylamino;

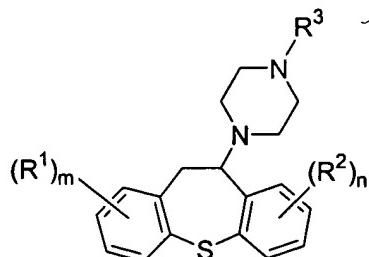
C_4)haloalkoxy, nitro, cyano, (C_1 - C_4)acyl, amino, (C_1 - C_4)alkylamino, and di(C_1 - C_4)alkylamino;

Z^1 is a divalent moiety selected from the group consisting of (C_1 - C_3)alkylene;

Z^2 is a divalent moiety selected from the group consisting of -O-, -S- and -N(R^3)- wherein R^3 is a member selected from the group consisting of H, halogen, (C_1 - C_4)alkyl, (C_1 - C_4)alkoxy, (C_1 - C_4)haloalkyl, (C_1 - C_4)haloalkoxy, nitro, cyano, (C_1 - C_4)acyl, amino, (C_1 - C_4)alkylamino, and di(C_1 - C_4)alkylamino; and

N^{Het} is a substituted or unsubstituted 4-, 5-, 6-, or 7-membered nitrogen heterocycle.

Claim 42 (new): A method of claim 41, wherein the compound has the formula:



wherein

the subscripts m and n are independently integers of from 0 to 3;

R^1 and R^2 are substituents independently selected from the group consisting of halogen, (C_1 - C_4)alkyl, (C_1 - C_4)alkoxy, (C_1 - C_4)alkylthio, (C_1 - C_4)haloalkyl, (C_1 - C_4)haloalkoxy, nitro, cyano, (C_1 - C_4)acyl, amino, (C_1 - C_4)alkylamino, and di(C_1 - C_4)alkylamino; and

R^3 is a substituent selected from the group consisting of (C_1 - C_4)alkyl, (C_1 - C_4)haloalkyl and (C_1 - C_4)acyl.

REMARKS/ARGUMENTS

Status of the Specification

As suggested by the Examiner, Applicants have amended the first paragraph of the specification to recite the priority claim set forth in the ADS. The paragraph is further amended to set forth the patent application numbers. corresponding to the recited applications.

In view thereof, Applicants believe no new matter is added and respectfully request entry of the above amendments.

Status of the Claims

Claims 5, 8-13, 29, and 31-40 remain pending and are presented for examination. Claims 41 and 42 are newly presented. After entry of these amendments, claims 5, 8 -13, 29. and 31-42 will be pending.

Claims 5, 8-13, 29, and 31-40 stand rejected as alleged not conforming to the requirements of 35 U.S.C. §103(a) over Protiva et al. (U.S. Patent No. 4,243,805) in view of the Merck Manual of Diagnosis and Therapy (17th Ed.) and Michelson (Eur. Cytokine Netw. 10(2): 286-287 (1999)).

Claims 29 and 31-40 stand rejected as alleged not conforming to the requirements of 35 U.S.C. §103(a) over Sindelar et al. in view of the Merck Manual of Diagnosis and Therapy (17th Ed.) and Michelson (Eur. Cytokine Netw. 10(2): 286-287 (1999)).

Applicants respond to the above rejections below.

Support for New Claims 41 and 42.

Support for the compound subject matter of new claims 40 and 41 is found *inter alia* in original claims 5 and 9. Support for the methods of treating CMV infection subject matter is found throughout the specification.

In view thereof, Applicants believe these amendments to the claims add no new matter and respectfully request their entry.

Rebuttals of the Prima Facie Cases for the Above Rejections

I. The Prima Facie Case Fails to Meet the Standard of Inherency Set Forth in the MPEP.

A principal issue to be resolved is the appropriate standard by which inherency should be judged in the obviousness context. With respect to obviousness under 35 U.S.C. §103(a), MPEP §2141.02, sets forth "Obviousness cannot be predicated on what is not known at the time an invention is made, even if the inherency of a certain feature is later established. *In re Rijckaert*, 9 F.2d 1531, 28 USPQ2d 1955 (Fed. Cir. 1993). See MPEP § 2112 for the requirements of rejections based on inherency." (see MPEP at 2100-122, paragraph bridging both columns). Applicants note that MPEP §2112, in turn, sets forth the requirements of rejection based on inherency thusly:

The express, implicit, and inherent disclosures of a prior art reference may be relied upon in the rejection of claims under 35 U.S.C. 102 or 103. "The inherent teaching of a prior art reference, a question of fact, arises both in the context of anticipation and obviousness." *In re Napier*, 55 F.3d 610, 613, 34 USPQ2d 1782, 1784 (Fed. Cir. 1995) (affirmed a 35 U.S.C. 103 rejection based in part on inherent disclosure in one of the references). See also *In re Grasselli*, 713 F.2d 731, 739, 218 USPQ 769, 775 (Fed. Cir. 1983).

Thus, the MPEP is in accord with the Examiner's position that an inherency rejection can apply in the nonobviousness determination. However, the MPEP further sets forth in this section (see MPEP starting at p. 2100-52 (Feb., 2003), first column, last three lines) that

The fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic. 1957 (Fed. Cir. 1993) (reversed rejection because inherency was based on what would result due to optimization of conditions, not what was necessarily present in the prior art); *In re Oelrich*, 666 F.2d 578, 581-82, 212 USPQ 323, 326 (CCPA 1981). "To establish inherency, the extrinsic evidence 'must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient.' " *In re Robertson*, 169 F.3d

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743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999) (citations omitted). (The claims were drawn to a disposable diaper having three fastening elements. The reference disclosed two fastening elements that could perform the same function as the three fastening elements in the claims. The court construed the claims to require three separate elements and held that the reference did not disclose a separate third fastening element, either expressly or inherently.).

"In relying upon the theory of inherency, the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art." *Ex parte Levy*, 17 USPQ2d 1461, 1464 (Bd. Pat. App. & Inter. 1990) (emphasis in original)."

There is thus simply no support in the MPEP for applying different standards of inherency in the anticipation and nonobviousness contexts. With respect to the instant rejections under 35 U.S.C. §103(a), it is unambiguous that inherency, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient to find inherency.

In framing the instant rejections the Examiner has not alleged that CMV is a principal or even very common cause of the great variety of CNS conditions which may be treatable with neuroleptic agents. Indeed, the CMV section in Merck is not within but *precedes* the section on CNS system viral diseases. Even within the realm of CMV pathology, CMV infection only very infrequently causes such CNS conditions posited by the Examiner as benefiting from neuroleptic therapy. The enclosed affidavit sets forth that CNS injuries of the kind posited by the Examiner are in fact an atypical consequence of *congenital* CMV infection occurring quite infrequently even in cases of *congenital* infections. None of the art cited by the Examiner suggests or discloses the advisability or utility of using neuroleptics *in utero* to treat any psychological or CNS condition in a *fetus*. Moreover, there are a great many nonviral causes of such conditions as mental retardation (e.g., toxins such as mercury or lead; nutritional deficiencies; genetic diseases such as trisomy 21; and simple physical trauma to the brain).

Nor, has the Examiner alleged or set forth *any* evidence that the compounds recited in the claims are necessarily or consistently selected for treating the subset of such

conditions which may present symptoms which may even remotely be suitable for treatment with a neuroleptic. Indeed, the enclosed page from the Physicians Desk Reference lists a great many antipsychotic drug alternatives of which only a small minority (2/13) read on the formula recited in the base claims¹.

Nor, as evidenced in the declaration of Brian McMaster, is the ability of a neuroleptic or psychotropic agent to bind the CMV US28 receptor common to such neuroleptic agents. Of such agents tested by the Applicants, only the structurally related octoclolohepin and methiothepin were found to be active. Applicants further call the Examiner's attention to the enclosed Declaration of Professor Mocarski of Stanford University which evidences further why one of skill in the art would not have considered neuroleptic agents reading on the compounds recited in the claims as being useful in treating CMV. Thus, the instant rejections under 35 U.S.C. §103(a) is based upon an application of a succession of mere possibilities and/or improbabilities and can not stand.

¹ Protiva teaches his compounds have antipsychotic properties which are typically associated with antidopaminergic or antiserotoninergic activity. Thus, the antipsychotic subsection of the psychotropic section of the PDR is a particularly apt comparison group.

Antipsychotics Identified in 1994 Physicians Desk Reference, 48th Edition.

Compound	Name	Reads on the formula	Structure is Found
Clozaril	Clozapine	No	Merck Index 2378 ^a
Compazine	Prochlorperazine	No	G & G, under phenothiazines ^b
Haldol	Haloperidol	No	G & G, last row of table
Loxitane	Loxapine	No	Merck Index 5404
Moban	Molindone hydrochloride	No	Merck Index 6086
Navane	Thiothixene	Yes	G & G, under thioxanthenes
Prolixin	Fluphenazine	No	G & G, under phenothiazines
Serentil	Mesoridazine	No	Merck Index 5755
Mellaril	Thioridazine	No	G & G, under phenothiazines
Stelazine	Trifluoperazine	No	G & G, under phenothiazines
Taractin	Chlorprothixene	yes	G & G, under thioxanthenes
Thorazine	Chlorpromazine	No	G & G, under phenothiazines
Trilafon	Perphenazine	No	G & G, under phenothiazines

^aMerck Index Tenth Edition 1983; ^bGoodman & Gilman The Pharmacological Basis of Therapeutics 5th Edition, 1975

Thus, under law and fact, the subject matter of the above claims conforms to the requirements of 35 U.S.C. §103(a). In view thereof, Applicants respectfully request that the above rejections be reconsidered and withdrawn.

II. Unexpected Results

The Examiner requests a side-by-side comparison of the subject matter of the prior art and the instant application. In response, the Applicants provide the following table.

Prior Art	Present Invention
Neuroleptic compounds of the subject formula specifically bind to dopaminergic and serotonergic receptors. see <i>Protiva</i> . No data in evidence to show <u>any</u> neuroleptic compounds bind to the US28 receptor or to suggest such activity for such compounds. Kindly consider the previously submitted remarks and those set forth in the Affidavit of Professor Mocarski bearing on this point.	Neuroleptic compounds of the subject formula specifically bind to the US28 receptor as opposed to other neuroleptic compounds. Data showing that such activity is not shared by all neuroleptic compounds ² .
US28 specifically binds large molecular weight chemokines involved in immune response.	

In view of the above, the Applicants respectfully request that the both grounds for rejection under 35 U.S.C. §103(a) be reconsidered and these rejections withdrawn.

² See Declaration of Brian McMaster setting forth in Appendix A therein a number of psychotropic agents of other formula which have similar binding properties with respect to dopamine and/or serotonin receptors as the compounds recited in claims 5 and 29 and which do not have the CMV US28 receptor activity of the compounds recited in claims 5 and 29.